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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,815	06/06/2002	Takehiko Koide	06478.1461	2579

22852 7590 03/02/2004

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EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	10/018,815	KOIDE, TAKEHIKO	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED Feb. 18, 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☐ The a)☐ affidavit, b)☐ exhibit, or c)☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☐ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: 1-9.

Claim(s) withdrawn from consideration: _____.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

The examiner acknowledges Response under 37 C.F.R. § 1.116 filed on February 18, 2004. Claim 2-9 are pending and are the subject of this Advisory Action.

DETAILED ACTION

1. Rejections

1.1. 35 USC, section 112, first paragraph

Lack of written description

Claim 2-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with written description requirement. The reasons are stated in the previous Office Action, Paper No. 10, in the final rejection and summarized herein.

The claims are directed to a human antithrombin variant characterized in that at least one of the amino acids at positions 78, 278, 378 and 380 are changed. The claims are directed to a large genus of human antithrombin variants, but the specification fails to describe thier structure. No single representative species of the genus is disclosed by presenting its amino acid sequence and its sequence identification number; neither the encoding gene of the polypeptide is given. Therefore, one skilled in the art does not know what amino acid sequence is to be modified so that its amino acids in positions 78, 278, 378 and 380 are substituted. Applicants do not disclose the amino acid sequence of antithrombin III that they mutated. The claimed muteins should be identified not only by their function but also by their structure.

In their Remarks Applicants point out that the specification identifies natural antithrombin III as a main control factor in the blood coagulation system etc. (page 2 lines 21-25 of the specification) whereas the natural mutants quoted by the examiner are inactive. This argument is persuasive. However, none of the information on page 2 refers to the structure of the antithrombin III that was mutated by Applicants. None of the prior art that discloses human wild type antithrobin III is incorporated in the specification by reference, or even mentioned on page 2. The claimed muteins should be identified not only by their function but also by their structure, this however is not the case. The claims, therefore remain rejected for lack of written description of structure.

3.4. 35 USC section 103

Claims 5 and 9 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Huntington J. A. et al. (Mechanism of Heparin Activation of Antithrombin. Evidence for Reactive Center Loop Preinsertion with Expulsion upon Heparin Binding, *Biochemistry*, 1996, 35, 8495-8503, and Conformational Conversion of Antithrombin to a Fully Activated Substrate of Factor Xa without Need for Heparin, *Biochemistry* 1998, 37, 3272-3277) and in view of common knowledge in molecular biology. The reasons were indicated in the previous Office Action, paper No. 10 and are reiterated herein.

Huntington et al. generated, by site directed mutagenesis, a variant of antithrombin wherein serine in position 380 is substituted by tryptophan (1996) or cysteine (1998); see the abstracts of both papers. Huntington et al. teach that position 380, having functional symbol P14, needs to be displaced from beta-sheet A of the

protein to render it heparin independent (page 3272 of 1998 paper, right column, line 33). On page 3274, left column line 9, Huntington et al. write: "We expressed a P14 S→C variant of antithrombin (S380C) to provide a means of introducing a bulky group at the P14 position by chemical modification and thus to lock the antithrombin in a conformation with the P14 residue exposed, rather than buried." The variants obtained by Huntington and co-workers indeed do not require heparin activation for its inhibitory function.

Huntington et al. do not teach substitution of residue 380 by other amino acids like alanine, aspartic acid, glycine, histidine, ileucine, leucine, asparagines, threonine, tyrosine, and valine that are recited in claim 5 and 9. However, it would have been obvious to one having ordinary skill in the art at the time of invention to have antithrombin and modify it to heparin independence by substituting the residue 380 by other amino acids particulary the ones which are bulky in comparison with serine, because the displacement of P14 from beta-sheet can be achieved by substitution of serine 380 by other bulky amino acid. Therefore, one skilled in the art would have use other amino acids than tryptophan and cysteine to produce other muteins with desired property, similarily as Huntington et al. previously did.

The motivation is provided by Huntington et al. who write, "This accounts both for the occurrence of thrombosis in patients whose antithrombin has a defect in heparin binding or activation and for the widespread clinical use of exogenous heparin as anticoagulant" (page 3272 of the 1998 paper, left column, line 20). Thus, one skilled in the art would be motivated to obtain antithrombin that is more clinically useful by making

it independent on its activator, heparin, by mutating position 380 and thus exposing P14 using several amino acids, and screening for the mutants having required property of heparin independence. The expectation of success was very high, because Huntington et al. teach that position 380, having functional symbol P14, needs to be displaced from beta-sheet A of the protein to render it heparin independent (page 3272 of 1998 paper, right column, line 33.), and Huntington et al. also teach how to achieve this displacement. The displacement can be achieved by substitution of serine 380 by other bulkier amino acids.

In their response in section A. No Motivation to Combine References, page 4, Applicants write, "While Huntington may provide motivation to create a clinically-useful variant by substituting cysteine at amino acid position 380, a person skilled in the art would not find motivation to try other amino acids, nor would such a person be motivated to try the 12 specific amino acids recited in claim 5 and 9." This argument of applicants is not found persuasive. Although not all of the 12 specific amino acids recited in claim 5 and 9 are obvious to give a heparine independent antithrombin when placed in position 380, Huntingtons data from both articles demonstrated that two amino acids that are bulkier than serine did the job.

In section B. No Reasonable Expectation of Success, Applicants argue that the probability of success in obtaining a heparine independent antithrombin was very low, only 10 % (two amino acids used by Hubtington et al. for substitution in position 380, versus the total of 20 amino acids). The probability of success is actually much higher,

if one takes into consideration that out of three amino acids that were in position 380, i.e., natural serine, and two man-substituted, cystine and tryptophan, two changed the natural antithrombin to heparin independent. Thus the probability of success strongly suggested by Huntington data was high, 2/3, i.e., 66%.

In summary, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Obtaining an antithrombin by placing Ala, Gly and Thr in position 380 is not obvious, because these amino acid are not bulkier than the native serine, however claim 5 and 9 are not limited to muteins containing in position 380 any one of Ala, Gly and Thr.

Applicants attention is turned to the article by Futumara et al. published after filing this application (Serine 380(P14) → Glutamte Mutation Activates Antithrombin as an Inhibitor of Factor Xa, J. Biol. Chem. 2000, 275, 4092-4098, included in IDS) providing further example that substituting serine in 380 position by an amino acid that is bulkier than serine renders the wild type antithrombin III heparin independent because it expels P14 from beta-sheet A; see the abstract.

Conclusion

None of the claims is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number

is (571) 272-0944 and the right fax number is (571) 273-0944. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m. EST.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (571) 272-0928. The fax phone number for this Group is (703)872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

Art Unit 1652

Patent Examiner

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